Risk of infections of biological and targeted drugs in patients with spondyloarthritis: meta-analysis of randomized clinical trials

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Abstract

Background: Concerns exist regarding the risk of infections in patients with spondyloarthritis (SpA) treated with biologics. We assessed the risk of infections of biological and targeted drugs in patients with SpA by performing a meta-analysis based on randomized controlled trials (RCTs).

Methods: A systematic literature search was conducted in PubMed, Embase, Web of Science, the Cochrane Library, and China Biology Medicine Disc for RCTs evaluating the risk of infections of biological therapy in patients with SpA from inception through August 9, 2021. We calculated a pooled Peto odds ratio (OR) for infections in biologics-treated patients *vs.* placebo patients. The risk of bias on the included RCTs was assessed by using the Cochrane Risk of Bias Tool.

Results: In total, 62 studies were included in this meta-analysis. Overall, the risk of infection (Peto OR: 1.16, 95% confidence interval [CI]: 1.07–1.26, P < 0.001), serious infection (Peto OR: 1.65, 95% CI: 1.26–2.17, P < 0.001), upper respiratory tract infection (URTI) (Peto OR: 1.17, 95% CI: 1.04–1.32, P = 0.008), nasopharyngitis (Peto OR: 1.25, 95% CI: 1.10–1.42, P < 0.001), and *Candida* infection (Peto OR: 2.64, 95% CI: 1.48–4.71, P = 0.001) were increased in SpA patients treated with biologics compared with placebo. Sensitivity analysis based on biologics classes was conducted, and results demonstrated that compared with placebo, there was a higher risk of infection for tumor necrosis factor (TNF)- α inhibitors (Peto OR: 1.38, 95% CI: 1.13–1.68, P = 0.001) and interleukin (IL)-17 inhibitors (Peto OR: 1.55, 95% CI: 1.08–2.22, P = 0.018) in axial SpA, and for Janus kinase inhibitors in peripheral SpA (Peto OR: 1.39, 95% CI: 1.14–1.69, P = 0.001); higher risk of serious infection for IL-17 inhibitors in peripheral SpA (Peto OR: 1.36, 95% CI: 1.26–9.55, P = 0.016) and axial SpA (Peto OR: 2.01, 95% CI: 1.38–2.91, P < 0.001); higher risk of URTI for TNF- α inhibitors in axial SpA (Peto OR: 1.37, 95% CI: 1.05–1.78, P = 0.019), and for apremilast in peripheral SpA (Peto OR: 1.60, 95% CI: 1.08–2.36, P = 0.018); higher risk of nasopharyngitis for TNF- α inhibitors in axial SpA (Peto OR: 1.41, 95% CI: 1.05–1.90, P = 0.022) and peripheral SpA (Peto OR: 1.49, 95% CI: 1.09–2.05, P = 0.013), and for IL-17 inhibitors in axial SpA (Peto OR: 1.35, 95% CI: 1.01–1.82, P = 0.044); higher risk of herpes zoster for Janus kinase inhibitors in peripheral SpA (Peto OR: 2.18, 95% CI: 1.03–4.62, P = 0.043); higher risk of herpes zoster for Janus kinase inhibitors in peripheral SpA (Peto OR: 2.52, 95% CI: 1.03–4.62, P = 0.043); higher risk of Candida infection for IL-17 inhibitors in peripheral SpA (Peto OR: 2.52, 95% CI: 1.03–4.62, P = 0.043); higher risk of Candida infection for IL-17 inh

Conclusions: This meta-analysis shows that biological therapy in patients with SpA may increase the risk of infections, including serious infections, URTI, nasopharyngitis, and *Candida* infection, which should be paid attention to in our clinical practice. **Keywords:** Spondyloarthritis; Biological therapy; Infection; Herpes zoster; Meta-analysis

Introduction

Spondyloarthritis (SpA) is a series of chronic inflammatory conditions that have a range of manifestations, including predominantly axial SpA (radiographic axial SpA [axSpA] and non-radiographic axial SpA) and peripheral SpA (enteropathic arthritis, reactive arthritis, and psoriatic arthritis).^[1] People with predominantly axSpA may have additional peripheral symptoms, and *vice versa*. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or conventional synthetic disease-modifying anti-rheumatic

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Quick Response Code:	Website: www.cmj.org			
	DOI: 10.1097/CM9.0000000000001928			

drugs (csDMARDs), or a combination of both, can usually ameliorate disease activity and retard joint damage, thereby improving the quality of life of patients with SpA. However, in a sizeable proportion of patients with SpA, NSAIDs, or csDMARDs fail or are not tolerated. For these patients not responding to NSAIDs or csDMARDs, biologics or small molecular targeted drugs can provide clinically important improvement via targeting specific inflammatory mediators in inflammatory pathways, alleviating inflammation, and thus better controlling symptoms and structural destruction.^[2,3]

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Chinese Medical Journal 2022;135(8)

Received: 02-07-2021; Online: 28-12-2021 Edited by: Lishao Guo

Concerns have been raised about the safety of biologics or small molecular targeted drugs, due to their immunosuppressive effects that may contribute to an increased risk of infections in these patients. In turn, the infections may further aggravate the symptoms of patients with SpA, which is the most contradiction in making biologics treatment decisions. Therefore, it is very important to make optimal decisions after weighing the benefits and risks of treatments based on the patient's individual conditions and to keep alert to the risk of developing serious infections during the treatments of biologics.

At present, many randomized controlled trials (RCTs) have reported the infections of biologics and small molecular targeted drugs in the treatment of SpA. However, RCTs are inadequate for detecting and quantifying a small number of events, such as viral and fungal infections, serious infections, and opportunistic infections. A meta-analytic approach is considered useful to overcome the inherent limitations of individual RCTs in the assessment of safety outcomes. The main objective of the systematic review is to summarize and contextualize the risk of infections accompanying biologics and small molecular targeted drugs use in RCTs via using meta-analysis.

Methods

We strictly followed the Preferred Reported Items for Systematic Reviews and Meta-analyses guidelines and the recommendations from the Cochrane Collaboration to conduct this systematic review and meta-analysis.^[4]

Data sources and searches

An information specialist and experienced medical librarian was invited to conduct a comprehensive literature search. The following electronic bibliographic databases: PubMed, Embase, the Cochrane Library, Web of Science, and the China Biology Medicine disc (CBM), were searched from inception through August 9, 2021. No limits were applied to race, sex, or language, except for human subjects. The details of search strategies for the electronic database were shown in Appendix 1, http:// links.lww.com/CM9/A879. Other resources were hand-searched, including websites and bibliographic references from RCTs and systematic reviews of interest, for additional citations not identified through the original search strategy.

Selection of the trials

Study inclusion was assessed by two pairs of independent researchers (Siliang Man and Xiaojian Ji, Yiwen Wang and Chuan Song). Disagreements were discussed and resolved through consensus and, when needed, a third researcher acted as an adjudicator (Lidong Hu) until a consensus was reached.

Eligible trials were required to (1) be RCTs comparing the safety (infections) of the biologics (tumor necrosis factor [TNF]- α inhibitors, interleukin (IL)-17 inhibitors, IL-6 inhibitors, IL-23 inhibitors, small molecule targeted drugs, and so on) against placebo, NSAIDs, or any csDMARD; (2)

include only patients with SpA including axial SpA and peripheral SpA; and (3) have at least one 12-week follow-up.

Data extraction and risk of bias assessment

Two reviewers (Siliang Man and Xiaojian Ji) independently extracted the data of each trial and the other two reviewers (Yiwen Wang and Jiaxin Zhang) checked the extracted results. Disagreements were discussed and solved through consensus, and a third reviewer acted as an adjudicator (Lidong Hu) if necessary. For each selected RCTs, we collected general information (eg, authors' name, publication year, country, and study design), study population (eg, age of patients and gender distribution), and intervention characteristics (details of intervention and control, duration of intervention, and follow-up). Primary outcome data was the number and type of infections.

All included trials were assessed for risk of bias by two reviewers (Siliang Man and Xiaojian Ji) with version 2 of the Cochrane Risk of Bias Assessment Tool.^[5] The following domains of individual trials were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases (including carryover, extreme baseline imbalance, and funding). We assessed the risk of bias using the categories of yes (low risk of bias), no (high risk of bias), and unclear (lack of information or uncertainty about potential bias).

Data synthesis and analysis

We identified the number of patients with at least one outcome of interest, based on the analysis of the adverse event in an individual trial. The number of patients with SpA receiving at least one dose of the study drug represented the denominator of our outcome measurement.

Our study protocol required the use of a fixed-effect model for meta-analysis due to its superior performance while pooling the clinical trials with a small number of events, and the results were expressed as Peto odds ratio (OR) and associated 95% confidence interval (CI). We stratified by biologics classes to explore how different biologics classes affect the risk of infections.

Meta-analysis was conducted using the "meta" package on R software (version 3.6.2 x64; The R Foundation for Statistical Computing). P value < 0.05 was considered a significant difference in all tests.

Results

Literature selection and trial characteristics

A total of 13,103 unique citations were identified through electronic bibliographic databases and hand-searching. There were 8925 records that were potentially relevant to our topic in our first selection round, of which 166 were deemed eligible for a full review. Finally, a total of 62 trials met inclusion criteria for this systematic review and metaanalysis. All the included studies were reported in Chinese or English. The details of the study selection process were shown in Supplementary Figure 1, http://links.lww.com/ CM9/A877.

The 62 RCTs containing 19,411 patients with SpA, were published between 2002 and 2021. Among these RCTs, 25 investigated axSpA and 37 investigated peripheral SpA. A majority of RCTs were two-arm clinical trials, with placebocontrolled periods ranging from 12 to 30 weeks (Supplementary Table 1, http://links.lww.com/CM9/A878).

Risk of bias assessments

Ninety percent of studies provided sufficient details of randomization. Although most of the clinical trials declared that they were double-blind, more than half of the trials indicated inadequate methods of allocation concealment. In all studies, the co-interventions and baseline characteristics were similar between the biologics group and control group (placebo, NSAIDs, and csDMARDs) were grouped together. In some patients who previously received TNF- α inhibitors, switching to other biologics (such as IL-17 inhibitors) might introduce a potential risk of bias. In some trials, the method of the imputation of no response, with "advancement penalty," was used to address this potential risk of bias. The risk of bias graph of assessment for all the included RCTs was demonstrated in Figure 1.

Serious infections

Serious infections were reported in 37 of 62 retrieved RCTs. Across these studies, the patients of serious infection with biological treatments and placebo were 236 (2.60%) and 82 (1.59%), respectively. The measurement of inconsistency between the RCTs (I^2) was 15% (P = 0.22), which indicated that there was no statistical heterogeneity in these trials. Overall, there was an increased risk of serious infections in patients with SpA using biological and targeted drugs *vs.* placebo (Peto OR 1.65, 95% CI: 1.26–2.17, P < 0.001; Figure 2).

Subgroup analysis of trials was conducted by using biologics classes. The risks of serious infections were

higher than placebo for IL-17 inhibitors in patients with peripheral SpA (Peto OR: 3.46, 95% CI: 1.26–9.55, P = 0.016; $I^2 = 0\%$, P = 0.87) and axial SpA (Peto OR: 2.01, 95% CI: 1.38–2.91, P < 0.001; $I^2 = 0\%$, P = 0.52). There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 2].

Common infections

Common infections were reported in 34 of 62 retrieved RCTs. Across these studies, the patients of infection with biological treatments and placebo were 2353 (27.55%) and 1208 (24.34%), respectively. Overall, there was an increased risk of infections in individuals with SpA using biological and targeted drugs *vs.* placebo (Peto OR 1.16, 95% CI: 1.07–1.26, *P* < 0.001), with low heterogeneity ($I^2 = 16\%$, P = 0.19) [Figure 3].

The subgroup analysis consisted of these RCTs providing data on different biologics classes. The results demonstrated that compared with placebo, there was a higher risk of infection for TNF- α inhibitors (Peto OR: 1.38, 95% CI: 1.13–1.68, P = 0.001; $I^2 = 0\%$, P = 1.00) and IL-17 inhibitors (Peto OR: 1.55, 95% CI: 1.08–2.22, P = 0.018; $I^2 = 0\%$, P = 0.90) in axial SpA, and for Janus kinase (JAK) inhibitors in peripheral SpA (Peto OR: 1.39, 95% CI: 1.14–1.69, P = 0.001; $I^2 = 0\%$, P = 0.91). There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 3].

Upper respiratory tract infection

Upper respiratory tract infection (URTI) was reported in 49 studies. Across these studies, the patients of URTI with biological treatments and placebo were 906 (7.30%) and 472 (6.78%), respectively. Overall, there was an increased risk of URTI in individuals with SpA using biological and targeted drugs *vs.* placebo (Peto OR 1.17, 95% CI: 1.04–1.32, P = 0.008), with low heterogeneity ($I^2 = 5\%$, P = 0.37) [Figure 4].

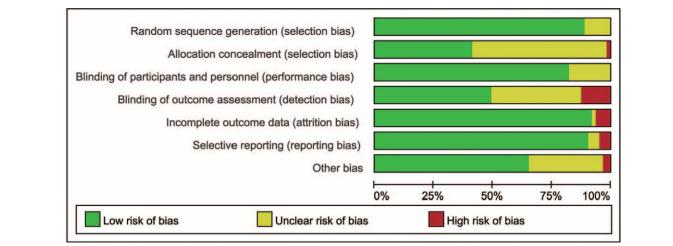


Figure 1: Risk of bias graph.

Subgroup = JAKI for pSpA Gladman D 2017 McInnes IB 2021 Mease P 2017 Fixed effect model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $\rho = 0.57$

milast for pSpA

neity: $l^2 = 16\%$, $\tau^2 = 0.1863$, $\rho = 0.31$

neity: $l^2 = 15\%$, $\tau^2 = 0.1431$, p = 0.22

ibgroup = Apre wanaugh A 2014

ase PJ 2020 alls AF 2018 and effect mo

Fixed effect model Heterogeneity: not app

Fixed effect model

Subgroup = Other for pSpA Mease P 2016

Study	Odds Ratio	OR		95%-CI	Weight	Study
Subgroup = IL-17i for pSpA	11					Subg
Baraliakos X 2020	÷ •	4.56	[0.94;	22.18]	2.9%	Carro
McInnes IB 2013		- 4.48	[0.07;	286.49]	0.4%	
Mease PJ 2014		0.98	[0.09;	11.07]	1.3%	Genov
Mease PJ 2016		4.56	[0.41:	50.371	1.3%	Kavan
Nash P 2017	- <u>+</u>	4.44	[0.39;	50.02]	1.3%	McInn
Fixed effect model	0	3.46	[1.26;	9.55]	7.2%	Mease
Heterogeneity: $t^2 = 0\%$, $\tau^2 = 0$, $p = 0.87$						Mease
Subgroup = IL-17i for axSpA						Mease
Baeten D1 2015		2.63	[1.59;	4.36]	28.9%	
Baeten D2 2015	*	1.25	[0.68;	2.30]	19.9%	Param
Deodhar A 2019		- 4.60	[0.07;	284.31]	0.4%	Torii H
Deodhar A 2021		4.51	[0.24;	85.24]	0.9%	Fixed
Huang F 2020	<u>+</u> ;	1.84	[0.29;	11.90]	2.1%	Hetero
van der Heijde D 2018		4.62	[0.25;	85,961	0.9%	
Fixed effect model	\$	2.01	[1.38;	2.91]	53.0%	Subgi
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$						Deodh
						Huang
Subgroup = TNFi for pSpA						Inman
Carron P 2017		0.84	[0.20;	3.49]	3.6%	Lande
Genovese MC 2007		0.13	[0.00;	6.55]	0.5%	
Kavanaugh A 2010		0.14	[0.02;	0.86]	2.3%	Lande
Kavanaugh A 2017		0.51	[0.05;	4.92]	1.4%	Douga
McInnes IB 2021		0.74	[0.17;	3.27]	3.3%	Sieper
Mease P 2017		10102031	310168	0400023	0.0%	van de
Mease PJ 2013	- <u> -</u>	1.83	[0.28;	11.85]	2.1%	van de
Mease PJ 2016	+	7.84	[0.49;	126.33]	1.0%	van de
Paramarta JE 2013		0.14	[0.00;	6.82]	0.5%	
Torii H 2010 -		0.06	[0.00;	3.53]	0.4%	Fixed
Fixed effect model Heterogeneity: $l^2 = 18\%$, $\tau^2 = 0.2713$, $\rho = 0.28$	•	0.63	[0.31;	1.26]	15.1%	Hetero
A 18 18						Subg
Subgroup = TNFi for axSpA						Deodh
Deodhar A 2018		- 7.25	[0.14;	365.43]	0.5%	Deodh
Huang F 2014		- 4.49	[0.07;	286.26]	0.4%	Mease
Inman RD 2008		0.50	[0.03;	7.88]	1.0%	Fixed
Landewé R 2013		4.46	[0.23;	85.55]	0.8%	
Landewé R 2018		0.14	[0.00;	6.87]	0.5%	Hetero
Dougados M 2014		0.14	[0.00;	6.94]	0.5%	
van der Heijde 2005		3.96	[0.17;	90.10]	0.8%	Subgr
van der Heijde 2006 -		0.05	[0.00;	3.30]	0.4%	Deodh
van der Heijde D 2018		- 7.07	[0.14;	356.56]	0.5%	Pavel
Fixed effect model	\Leftrightarrow	1.20	[0.37;	3.89]	5.3%	van de
Heterogeneity: I ² = 3%, τ ² = 0.0958, p = 0.41	1					
						Fixed
Subgroup = IL-23i for pSpA						Hetero
Deodhar A 2018	· · · · · · · · · · · · · · · · · · ·	- 4.44	[0.07;	287.70]	0.4%	
Deodhar A 2020		0.05	[0.00;	0.92]	0.8%	Subgr
Mease PJ 2020		1.83	[0.28;	11.78]	2.1%	McInn
Fixed effect model		0.82	[0.19;	3.59]	3.4%	McInn
Heterogeneity: I ² = 59%, τ ² = 3.0700, p = 0.09						Mease
2 7 No. 10120 Trail 2 Tr						
Subgroup = JAKi for Axial SpA		2020		0239999770		Mease
Deodhar A 2020		- 7.56	[0.15;	380.97]	0.5%	Mease
Fixed effect model		7.56	[0.15;	380.97]	0.5%	Nash
Heterogeneity: not applicable						Fixed

4.49 1.83

1.99

2.56 4.52 1.82

1 65

Favouring Placebo

[0.24; [0.72;

[0.81:

[0.06 [0.58; [0.41; [0.62;

[1.26;

0.8% 8.4% 0.0% 9.2%

1.7% 3.4% 1.3% 6.3% 3.78

0.0%

2.171 100.0%

85.41] 4.67]

4.851

11.25

Study	Odds Ratio	OR	95	%-CI	Weigh
Subgroup = TNFi for pSpA	8				
Carron P 2017		0.84	[0.20;	3.49]	0.3%
Genovese MC 2007		0.45	[0.18;		0.9%
Kavanaugh A 2017		1.26	[0.78;	2 021	3.1%
McInnes IB 2021	and a	1.04	[0.78;		8.8%
Mease P 2017		0.51	[0.05;		0.1%
Mease PJ 2004		0.90	[0.49;		1.9%
Mease PJ 2004 Mease PJ 2013	1:				
Mease PJ 2013 Mease PJ 2016	17	1.16	[0.76;		4.0%
		1.01	[0.54;	1.89]	1.8%
Paramarta JE 2013		0.40	[0.10;		0.4%
Torii H 2010			[1.71; 1		0.6%
Fixed effect model Heterogeneity: $I^2 = 40\%$, $\tau^2 = 0.0640$, $p = 0.09$	Ê	1.06	[0.88;	1.27]	22.0%
Subgroup = TNFi for axSpA					
Deodhar A 2018		1.52	[0.61;	3 821	0.8%
Huang F 2014		1.05	[0.51;		1.4%
Inman RD 2008		1.56	[0.94;		2.8%
Landewé R 2013		1.26	[0.66;		1.7%
	1				
Landewé R 2018	17-	1.32	[0.84;		3.5%
Dougados M 2014		1.13	[0.46;	2.78]	0.9%
Sieper J 2013		1.33	[0.58;		1.0%
van der Heijde 2005		1.31	[0.77;	2.25]	2.4%
van der Heijde 2006	÷ *	1.65	[0.99;	2.77]	2.7%
van der Heijde D 2018		1.49	[0.70;	3.21]	1.2%
Fixed effect model	0	1.38	[1.13;	1.68]	18.4%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 1.00$					
Subgroup = IL-23i for pSpA					
Deodhar A 2018		0.74	[0.30;	1.811	0.9%
Deodhar A 2020		0.98	[0.60;		2.9%
Mease PJ 2020		0.98	[0.66;		4.5%
Fixed effect model	4		[0.71;		8.3%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$		10000	1		
Subgroup = IL-17i for axSpA					
Deodhar A 2019	÷	1.68	[1.03;	2,741	2.9%
Pavelka K 2017		1.46	[0.62;		1.0%
van der Heijde D 2018		1.39	[0.71;		1.6%
Fixed effect model	1		[1.08;		5.5%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.90$,	
Subgroup = IL-17i for pSpA					
McInnes IB 2013		1.33	[0.37;	4.74]	0.4%
McInnes IB 2015		0.85	[0.52;	1.42]	2.8%
Mease P 2018		0.82	[0.53;	1.271	3.7%
Mease PJ 2015	-	1.38	[0.95;	2.011	5.0%
Mease PJ 2016		1.02	[0.60;		2.5%
Nash P 2017			[0.92;	2 311	3.4%
Fixed effect model	4	1.11			17.7%
Heterogeneity: $l^2 = 12\%$, $\tau^2 = 0.0092$, $p = 0.34$	Ĩ		[0.01,	1.00]	11.17
Subgroup = Other for pSpA					
McInnes IB 2013		0.84			3.9%
Mease P 2016		0.49	[0.24;		1.3%
Mease PJ 2017		0.86	[0.56;		4.0%
Fixed effect model	•		[0.59;		
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.40$					
Subgroup = JAKi for pSpA					
McInnes IB 2021		1.41	[1.11;	1.80]	12.4%
Mease P 2017		1.00	[0.18;	5.521	0.2%
Mease PJ 2020		1.36	[0.97;		6.3%
Fixed effect model		1.39	[1.14;		18.9%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$			·		
Fixed effect model		1.16	[1.07;	1.26]	100.0%
Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0.0140$, $p = 0.19$					
	0.1 0.5 1 2 1				
Favor	uring Biologics Favouring	riacebo			

Figure 2: Forest plot of meta-analyses comparing biologics vs. placebo for risk of serious infections. OR: Odds ratio.

0.1 10 1000

1

0.001

Favouring Biologics

The subgroup analysis, based on different biologics classes, demonstrated a higher risk of URTI for TNF-a inhibitors in axial SpA (Peto OR: 1.37, 95% CI: 1.05–1.78, P = 0.019; $I^2 = 24\%$, P = 0.20) and for apremilast in peripheral SpA (Peto OR: 1.60, 95% CI: 1.08–2.36, P = 0.018; $I^2 = 46\%$, P = 0.10), compared with placebo. There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 4].

Nasopharyngitis

Nasopharyngitis was reported in 40 studies. Across these studies, the patients of nasopharyngitis with biological treatments and placebo were 792 (7.56%) and 356 (6.03%), respectively. Overall, patients with SpA treated with biological and targeted drugs showed an increased risk of nasopharyngitis than placebo (Peto OR 1.25, 95% CI 1.10–1.42, P < 0.001), with low heterogeneity $(I^2 = 0\%, P = 0.54)$ [Figure 5].

The subgroup analysis, based on different biologics classes, demonstrated a higher risk of nasopharyngitis for TNF- α inhibitors in peripheral SpA (Peto OR: 1.49, 95% CI: 1.09–2.05, P = 0.013; $I^2 = 0\%$, P = 0.73) and axial SpA (Peto OR: 1.41, 95% CI: 1.05–1.90, P = 0.022; $I^2 = 0\%$, P = 0.88), and for IL-17 inhibitors in axial SpA (Peto OR: 1.35, 95% CI: 1.01–1.82, P = 0.044; $I^2 = 9\%$, P = 0.36). There was no significant difference between other biologics and placebo in patients with peripheral SpA and axial SpA [Figure 5].

Candida infection

Candida infection (high-level term) was reported in 14 studies. Overall, patients with SpA treated with biologics showed an increased risk of Candida infection than placebo (Peto OR 2.64, 95% CI: 1.48–4.71, P = 0.001), with low heterogeneity ($I^2 = 0\%$, P = 0.81) [Figure 6]. The subgroup analysis, based on different biologics classes,

ÓR

95%-CI Weight

Study	Odds Ratio	OR	95%-CI	Weight	Study
Subgroup = IL-17i for pSpA Baraliakos X 2020		0.79	10.051 0.541	1.0%	Subgroup = TNFi for pS
McInnes IB 2015		1.03	[0.25; 2.54] [0.43; 2.48]	1.8%	Antoni C 2005 Kavanaugh A 2010
Mease P 2018		0.70	[0.42; 1.16]	5.3%	McInnes IB 2021
Mease PJ 2014		1.60	[0.55; 4.64]	1.2%	Mease P 2017
Mease PJ 2015	<u>_k</u> _	1.10	[0.52; 2.35]	2.4%	Mease PJ 2004
Mease PJ 2016		0.54	[0.18; 1.63]	1.1%	Mease PJ 2013
Nash P 2017		1.24	[0.57; 2.70]	2.3%	Mease PJ 2016
Nash P 2018		1.28	[0.47; 3.50]	1.4%	Torii H 2010
Fixed effect model	\$	0.93	[0.70; 1.25]		Fixed effect model
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.73$					Heterogeneity: $l^2 = 0\%$, $\tau^2 =$
Subgroup = IL-17i for axSpA		1 42	10 19: 11 641	0.2%	Subgroup = IL-17i for as
Baeten D1 2015			[0.18; 11.64]	0.3%	Baeten D1 2015
Baeten D2 2015 Deodhar A 2019		4.53	[0.07; 285.45] [0.53; 5.43]	0.1%	Baeten D2 2015
Deodhar A 2019 Deodhar A 2021	1	1.56	[0.53, 5.43]		Deodhar A 2019
Huang F 2020	1 cm	1.23		6.1%	Deodhar A 2021
van der Heijde D 2018	_ <u>F</u>	1.44		1.1%	Huang F 2020
Fixed effect model	6	1.37	[0.96; 1.95]	10.9%	Pavelka K 2017
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$					van der Heijde D 2018 Fixed effect model
Subgroup = TNFi for axSpA		0.07	10 17 1 000	0.70	Heterogeneity: $I^2 = 9\%$, $\tau^2 =$
Bao C 2014	-	0.97		2.7%	Subgroup = IL-17i for ps
Braun J 2002		0.52	[0.20; 1.35] [1.01; 3.66]	1.5%	Baraliakos X 2020
Davis JC 2003 Deodhar A 2018	1			1.6%	McInnes IB 2015
Haibel H 2008		1.52	[0.61; 3.82] [1.06; 10.47]	1.1%	Mease PJ 2014
Inman RD 2008	i	1.60	[0.73; 3.51]	2.2%	Mease PJ 2015
Inman RD 2008			[0.75; 73.47]		Mease PJ 2016
Landewé R 2013		1.59	[0.49; 5.16]	1.0%	Nash P 2017
Landewé R 2018		1.76	[0.85; 3.65]	2.6%	Nash P 2018
Marzo-Ortega H 2005		0.45	[0.05; 3.86]	0.3%	Fixed effect model
van der Heijde 2005	_ 	0.94	[0.44; 2.00]	2.4%	Heterogeneity: $l^2 = 51\%$, τ^2
van der Heijde D 2018		0.48	[0.09; 2.44]	0.5%	
Huang F 2011			[0.60; 24.77]	0.4%	Subgroup = Apremilast
Fixed effect model	ø	1.37	[1.05; 1.78]	19.9%	Cutolo M 2016
Heterogeneity: $I^2 = 24\%$, $\tau^2 = 0.0779$, $p = 0.20$	6				Edwards CJ 2016
	1				Nash P 2018
Subgroup = TNFi for pSpA	E				Schett G 2012
Antoni C 2005		0.65	[0.30; 1.44]		Fixed effect model
Carron P 2017	1			0.0%	Heterogeneity: $I^2 = 17\%$, τ^2
Genovese MC 2007		1.76			
Kavanaugh A 2010		1.63	[0.77; 3.47]		Subgroup = TNFi for axS
McInnes IB 2021		0.86			Davis JC 2003
Mease P 2017		0.59	[0.14; 2.42]	0.7%	Inman RD 2008
Mease PJ 2004	 F	0.88	[0.45; 1.69]	3.2%	Landewé R 2013
Mease PJ 2013		1.74	[0.81; 3.74]	2.4%	Landewé R 2018
Mease PJ 2016 Paramarta JE 2013		0.74	[0.23; 2.37]	1.0%	Sieper J 2013
Fixed effect model	E.		[0.78; 1.34]	18.6%	van der Heijde 2005
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.54$	Ĩ	1.02	[0.10, 1.04]	10.076	van der Heijde 2006
Therefogenerity. T = 0.0, T = 0, p = 0.04	6				van der Heijde D 2018
Subgroup = Apremilast for pSpA	E				Huang F 2010
Cutolo M 2016	÷	1.92	[0.89; 4.16]	2.3%	Fixed effect model
Edwards CJ 2016		2.80	[1.21; 6.47]	2.0%	Heterogeneity: $I^2 = 0\%$, $\tau^2 =$
Kavanaugh A 2014	-1=	1.41	[0.58; 3.41]	1.8%	
Nash P 2018		0.45	[0.16; 1.23]	1.3%	Subgroup = IL-23i for p
Schett G 2012	-	4.62	[0.71; 30.21]	0.4%	Deodhar A 2018
Wells AF 2018		1.58	[0.57; 4.41]		Deodhar A 2020
Fixed effect model	\$	1.60	[1.08; 2.36]	9.1%	Mease PJ 2020
Heterogeneity: $l^2 = 46\%$, $\tau^2 = 0.2109$, $p = 0.10$					Fixed effect model Heterogeneity: $J^2 = 0\%$, $\tau^2 =$
Subgroup = IL-23i for pSpA					
Deodhar A 2018			[0.02; 8.84]	0.2%	Subgroup = JAKi for axS
Deodhar A 2020		1.12	[0.48; 2.60]	1.9%	Deodhar A 2020
Mease PJ 2020	-	1.12	[0.49; 2.58]	2.0%	Fixed effect model
Fixed effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$	Ŷ	1.08	[0.61; 1.94]	4.1%	Heterogeneity: not applicable
					Subgroup = JAKi for pS
Subgroup = JAKi for axSpA	1	1.10	10.04	0.00	Gladman D 2017
Deodhar A 2020			[0.64; 3.41]		McInnes IB 2021
Fixed effect model	-	1.48	[0.64; 3.41]	2.0%	Mease P 2017
Heterogeneity: not applicable	:				Mease PJ 2020
	1				Fixed effect model
Subgroup = JAKi for pSpA Gladman D 2017	£	4.00	10 50. 0.041	4 70/	Heterogeneity: $I^2 = 10\%$, τ^2
McInnes IB 2021			[0.53; 3.31]		
Mease P 2017		0.67	[0.82; 1.84] [0.20; 2.29]	8.5% 0.9%	Subgroup = Other for pS
Mease PJ 2017 Mease PJ 2020	1	1.73		3.4%	Mease PJ 2017
Fixed effect model	E.		[0.92; 3.28] [0.95; 1.76]		Ritchlin C 2014
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.58$		1.29	[0.00, 1.76]	1 .4.49 70	Fixed effect model
					Heterogeneity: $I^2 = 32\%$, τ^2
Subgroup = Other for pSpA					Fixed effect model
McInnes IB 2013			[0.29; 1.62]	1.8%	Heterogeneity: $I^2 = 0\%$, $\tau^2 =$
Mease PJ 2017			[0.17; 1.05]	1.7%	
Ritchlin C 2014		1.01		0.9%	
Fixed effect model	*	0.62	[0.36; 1.08]	4.5%	
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$					Figure 5: Forest plot
Final effect model		4.17	14 04. 4 000	400.00/	
Fixed effect model Heterogeneity: $l^2 = 5\%$, $\tau^2 = 0.0100$, $p = 0.37$	r - 1 - 1	7 1.17	[1.04; 1.32]	100.0%	nasopharyngitis. OR: 0
	0.01 0.1 1 10 1	100			
Favou	ring Biologics Favouring	Placebo			
gure 4: Forest plot of meta-analyses c	omparing biologics	<i>vs.</i> plac	ebo for ris	k of URTI.	(Peto OR 2.18
		P. 199			

Figure 4: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of URTI. OR: Odds ratio; URTI: Upper respiratory tract infection.

demonstrated a higher risk of *Candida* infection for IL-17 inhibitors in peripheral SpA (Peto OR: 2.52, 95% CI: 1.31–4.84, P = 0.006; $I^2 = 0\%$, P = 0.64) [Figure 6].

Herpes zoster

Herpes zoster was reported in eight studies. The results of the meta-analysis showed an increased risk of herpes zoster for JAK inhibitors in peripheral SpA than placebo

Study	Ouus Natio	UN		10 01	morgin	
Subgroup = TNFi for pSpA	li li					
Antoni C 2005		1.30	[0.40;	4 251	1.2%	
Kavanaugh A 2010	im-	2.04	10.93		2.7%	
McInnes IB 2021	<u></u>	1.38	[0.78;		5.0%	
Mease P 2017	E	1.66	[0.41;	6.801	0.8%	
Mease PJ 2004		0.76	[0.26;	2 251	1.4%	
Mease PJ 2013	- <u>in</u>	1.36	[0.66;		3.2%	
Mease PJ 2016		1.50	[0.47;		1.2%	
Torii H 2010			[1.04;	16 191	0.9%	
Fixed effect model	6	1.49		2 051	16.2%	
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.73$		1.40	11.00,	2.00]	10.4.70	
Tieterogeneity, 1 = 016, t = 0, p = 0.75	1					
Subgroup = IL-17i for axSpA	1					
Baeten D1 2015	- lan	1.64	[0.81;	3 321	3.3%	
Baeten D2 2015		2.18	[0.77;		1.5%	
Deodhar A 2019		2.20	[1.11;	4 371	3.5%	
Deodhar A 2021		1.01	[0.59]		5.7%	
Huang F 2020		0.79			2.3%	
Pavelka K 2017	- 	2.04	[0.57;	7.36]	1.0%	
van der Heijde D 2018		0.96			1.5%	
Fixed effect model			[1.01;	1.821	18.8%	
Heterogeneity: $I^2 = 9\%$, $\tau^2 = 0.0166$, $p = 0.36$			1		1010.00	
fielding filler and filler and for the filler						
Subgroup = IL-17i for pSpA						
Baraliakos X 2020		0.55	[0.23;	1 321	2.2%	
McInnes IB 2015		0.61	[0.23;	1.59]	1.8%	
Mease PJ 2014	I	0.05	[0.00;		0.3%	
Mease PJ 2015	-	1.78	[0.91;		3.7%	
Mease PJ 2016		1.01	[0.34;		1.4%	
Nash P 2017		1.43			1.4%	
Nash P 2018		0.90			3.2%	
Fixed effect model	4	0.95			13.8%	
Heterogeneity: $l^2 = 51\%$, $\tau^2 = 0.2356$, $\rho = 0.06$		0.00	foroni	110-1	101070	
inerere and in a second a second by second						
Subgroup = Apremilast for pSpA						
Cutolo M 2016		1.30	[0.52;	3 241	2.0%	
Edwards CJ 2016		2.28	[0.71;	7.34]	1.2%	
Nash P 2018		1.31	[0.47;		1.6%	
Schett G 2012		0.61	[0.26;		2.3%	
Fixed effect model	-	1.12			7.0%	
Heterogeneity: $l^2 = 17\%$, $\tau^2 = 0.0504$, $\rho = 0.31$			1			
Subgroup = TNFi for axSpA						
Davis JC 2003	<u></u>	0.89	[0.33;	2.37]	1.7%	
Inman RD 2008		1.22	[0.58;		3.0%	
Landewé R 2013		1.55	[0.69;	3.48]	2.5%	
Landewé R 2018	-	1.31	[0.69;	2.46]	4.1%	
Sieper J 2013		1.38	[0.45;	4.25]	1.3%	
van der Heijde 2005		2.75	[1.05;	7.17]	1.8%	
van der Heijde 2006	- 1981 -	1.68	[0.79; [0.30;	3.56]	2.9%	
van der Heijde D 2018		0.95	[0.30;	3.07]	1.2%	
Huang F 2010		2.07	[0.21; 3	20.26]	0.3%	
Fixed effect model	\$	1.41	[1.05;	1.90]	18.7%	
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.88$						
	1					
Subgroup = IL-23i for pSpA						
Deodhar A 2018		0.54	[0.15;		1.0%	
Deodhar A 2020		1.43	[0.65;		2.7%	
Mease PJ 2020	-#-	1.22	[0.57;		2.8%	
Fixed effect model		1.16	[0.70;	1.91]	6.4%	
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.45$						
Cuberrow - 181/ fee - Co.A	8					
Subgroup = JAKi for axSpA	ji.	0.01	10.00	0.001	1.9%	
Deodhar A 2020			[0.36;			
Fixed effect model	-T-	0.91	[0.36;	2.32]	1.9%	
Heterogeneity: not applicable	1					
Subgroup = JAKi for pSpA	1					
Gladman D 2017	1	2.37	[0.91;	6 161	1.8%	
	i				6.0%	
McInnes IB 2021 Mease P 2017	12	1.12	[0.66; [0.50;		1.2%	
Mease PJ 2020		0.86	[0.46;		4.1%	
Fixed effect model	L	1.18			13.1%	
Heterogeneity: $l^2 = 10\%$, $\tau^2 = 0.0165$, $p = 0.34$	T.	1.10	foron!	1.00]	1.5.170	
(1010) (1010), 1 = 1010, 1 = 0.0100, p = 0.04	1					
Subgroup = Other for pSpA	E					
Mease PJ 2017		0.80	[0.33;	1 971	2.0%	
Ritchlin C 2014		1.76	[0.33,		2.0%	
Fixed effect model	—		[0.63;		4.0%	
Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.0984$, $p = 0.23$	T		10.00,	A.6.7]	4.070	
	E					
Fixed effect model	6	1.25	[1.10:	1.421	100.0%	
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.54$			1			
	0.01 0.1 1 10 100					
Fa	vouring Biologics Favouring Pla	cebo				
					or rick	
nuro 5, Earact plat of mata apoly	1000 comparing higlogics					

Odds Ratio

Figure 5: Forest plot of meta-analyses comparing biologics vs. placebo for risk of nasopharyngitis. OR: Odds ratio.

(Peto OR 2.18, 95% CI: 1.03–4.62, P = 0.043), with low heterogeneity ($I^2 = 0\%$, P = 0.77) [Figure 7].

Publication bias

Potential publication bias for serious infection as the primary outcome was assessed by visual inspection of funnel plot for asymmetry and Begg's test. The result showed that the funnel plot was symmetrical and no evidence of publication bias was found [Supplementary Figure 2, http://links.lww.com/CM9/A877]. The same result was also reflected in Begg's test (z = -0.71, P = 0.477).

Study	Odds Ratio	OR	95%-CI Weight	
Subgroup = IL-17i for pSpA Baraliakos X 2020 McInnes IB 2015 Mease P 2018 Mease PJ 2015 Mease PJ 2016 Nash P 2017 Nash P 2018 Fixed effect model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$		3.90 1.66 4.50 4.54 4.53 0.46	[0.39; 11.75] 11.5% [0.97; 15.65] 17.4% [0.41; 6.66] 17.3% [0.41; 49.87] 5.8% [0.24; 85.60] 3.9% [1.02; 20.18] 15.0% [0.06; 3.75] 7.7% [1.31; 4.84] 78.5%	
Subgroup = IL-17i for axSpA Baeten D1 2015 Baeten D2 2015 Deodhar A 2019 Huang F 2020 Pavelka K 2017 van der Heijde D 2018 Fixed effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.42$		4.53 0.05 4.54 4.51	[0.07; 287.71] 1.9% [0.07; 285.45] 1.9% [0.00; 3.39] 2.0% [0.57; 36.48] 7.7% [0.24; 85.91] 3.9% 0.0% [0.69; 10.98] 17.4%	
Subgroup = TNFi for axSpA Marzo-Ortega H 2005 van der Heijde D 2018 Fixed effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.88$		7.07	[0.07; 286.49]1.9%[0.14; 356.56]2.2%[0.33; 98.86]4.1%	
Subgroup = TNFi for pSpA Mease PJ 2016 Fixed effect model Heterogeneity: not applicable Fixed effect model		2.64	0.0% 0.0% [1.48; 4.71] 100.0%	
	0.001 0.1 1 10 100 avouring Biologics Favouring Place			
Figure 6: Forest plot of meta-analyses comparing biologics vs. place	oo for risk of Candida infection. OR: Odds ratio.			

Discussion

There has been concern regarding a putative increasing risk of infections with either biological or small molecular targeted drugs treatment because of the impacts of these therapies on the immune system. This systematic review and meta-analysis covered 62 published RCTs including 19,411 patients with SpA. The crude pooled results showed that there was an elevated risk of infections, including serious infections, URTI, nasopharyngitis, *Candida* infection, and herpes zoster, in patients with SpA receiving biologics and/or small molecular targeted drugs therapy, compared with placebo.

Stratified according to the treatment with biologics by different types of biological agents in each SpA type, we found that the risk of serious infections was higher for patients with peripheral SpA and axial SpA treated with IL-17 inhibitors during the placebo-controlled periods.

IL-17, as a pro-inflammatory cytokine, plays a vital role in mediating autoimmune inflammatory diseases, but it also plays a very important role in defense against infection caused by extracellular pathogens.^[6-8] A study demonstrated a reduced survival and increased bacterial burden in *IL-17A^{-/-}* mice infected with *Klebsiella pneumoniae* and severely impaired neutrophil levels in the lung. This was related to the decrease of CXC chemokines and granulocyte colony-stimulating factor (G-CSF) in bronchoalveolar lavage fluid.^[9] Another study showed an independent requirement for IL-23 in pulmonary host defense against infection of *K. pneumoniae*, which was required for IL-17 production.^[10] Besides, IL-17 is also important for protection against intracellular bacteria. Studies demonstrated that infections with *Francisella tularensis* and *Chlamydia* required the involvement of IL-17, the former of which was regulated through the induction of IL-12 and interferon- γ mediated by IL-17 in macrophages, linking Th1 and Th17 responses *in vivo*.^[11,12]

Study	Odds Ratio	ÓR	95%-CI Weight
Subgroup = IL-17i for axSpA Deodhar A 2019		1.05	[0.10; 11.46] 8.0%
Fixed effect model			[0.10; 11.46] 8.0%
Heterogeneity: not applicable		1100	[erro, rrivo] ereve
Subgroup = JAKi for axSpA			
Deodhar A 2020			0.0%
Fixed effect model			0.0%
Heterogeneity: not applicable			
Subgroup = JAKi for pSpA			
Gladman D 2017	- <u>Li =</u>	4.49	[0.24; 85.41] 5.3%
McInnes IB 2021	- <u>-</u> -	1.45	[0.43; 4.85] 31.3%
Mease P 2017	- <u>+</u>	4.54	
Mease PJ 2020		2.26	[0.70; 7.25] 33.5%
Fixed effect model	-	2.18	[1.03; 4.62] 80.5%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.77$			
Subgroup = TNFi for axSpA			
Marzo-Ortega H 2005		4.48	[0.07; 286.49] 2.6%
Fixed effect model		4.48	[0.07; 286.49] 2.6%
Heterogeneity: not applicable			
Subgroup = TNFi for pSpA			
McInnes IB 2021		0.13	[0.01; 1.28] 8.9%
Mease P 2017			0.0%
Fixed effect model		0.13	[0.01; 1.28] 8.9%
Heterogeneity: not applicable			
Fixed effect model	-	1.63	[0.83; 3.21] 100.0%
Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.1205$, $p = 0.34$			
And a second state state of the second state o	0.01 0.1 1 10 100		
Fa	vouring Biologics Favouring Pla	cebo	
Figure 7: Forest plot of meta-analyses comparing biologics vs. placebo for	risk of herpes zoster. OR: Odds ratio.		

In addition, in our study, we found a higher risk of Candida infection for IL-17 inhibitors in peripheral SpA. IL-17 plays an important protective role in the setting of fungal infections. Two mouse models infected with oropharyngeal Candida indicated that IL-17 and IL-23 played a very important role in defense against mucosal C. albicans. Furthermore, microarray analysis demonstrated that after immunocompetent wild-type mice were infected with C. albicans, expression of many classical IL- 17 target genes in the oral mucosa was upregulated, including beta-defensin 3, G-CSF, IL-6, matrix metalloproteinase-8, chemokine CXCL1, and CXCL5.^[13] Another study showed that the release of IL-17 upon stimulation with Candida in peripheral blood mononuclear cells from the patients with acute Candida infection was significantly higher than the healthy control. These indicated the importance of IL-17 in protecting the host from *Candida* infection.^[14]

Therefore, mechanistically, treatment with IL-17 inhibitors may increase the risk of these infections. However, in our study, there may be a bias for risk evaluation of infections due to the complexity of the condition. As second-line therapy, secukinumab or ixekizumab is recommended over the use of a second TNF- α inhibitor in patients with primary non-response to the first TNF- α inhibitors according to the ACR/SAA/SPARTN treatment guideline.^[15] These patients may have more severe and refractory conditions. Of the included studies on IL-17 inhibitors, 10 (66.7%) studies allowed the patients previously treated with TNF- α inhibitors if they had no adequate response or stopped treatment due to safety or tolerability reasons. Since the detailed information on individuals previously exposed to biologics were not reported, it was difficult to perform further subgroup analysis. In addition, IL-17 inhibitors have been on the market for a relatively short time, and there is less evidence of their adverse events. Therefore, the risk of infections needs to be assessed through more studies and longer follow-up.

Treatment with TNF- α inhibitors showed an increased risk of common infections in patients with axial SpA. However, the results did not suggest a significantly higher risk of serious infections in patients with peripheral SpA and axial SpA treated with TNF- α inhibitors compared with placebo, which was in line with previous studies.^[16,17] Among the patients with common infections identified, the majority were minor, especially URTI and nasopharyngitis. With more studies included and consistent results with the previous meta-analyses, our findings are robust to some extent and it is unlikely that new clinical trials will affect the conclusion of this analysis.

In our study, another important finding was that JAK inhibitors had a significantly increased risk of herpes zoster in patients with peripheral SpA. Patients with some immune-mediated inflammatory diseases intrinsically have an increased risk of herpes zoster infection.^[18,19] This risk will further increase in patients treated with JAK inhibitors.^[20-22] According to clinical trials and real-world data, patients starting JAK inhibitors or other biologics for rheumatoid arthritis had similar rates of adverse events, including serious infection, but JAK inhibitor initiators had a higher incidence of herpes zoster than other biologics initiators.^[20,21] The most characteristic infectious complication with JAK inhibitors is herpes zoster caused by the reactivation of the varicella-zoster virus. The possible mechanism is that the immune response to the varicellazoster virus is partially mediated through the JAK-STAT pathway. In addition, patients with deficiencies in natural killer cell function are susceptible to infection with the varicella-zoster virus. The development and activation of natural killer cells also depend on cytokines mediated through the JAK-STAT pathway. Besides, dose-dependent reductions in peripheral blood natural killer cell counts have been reported for all JAK inhibitors.^[23]

There are several study limitations to consider. First, the short period of exposure in the included RCTs is a major solid limitation. Therefore, our results can only represent short-term or medium-term risk assessment of infections using biologics. Second, definitions of infections may differ by individual studies, and many studies did not strictly follow the standard definition of infections within the Medical Dictionary for Regulatory Activities dictionary. These cases were collected based on the original publication case description only with relevant differences between studies. These may result in an increased heterogeneity to a certain extent in collecting these cases. Third, csDMARDs and corticosteroids may further increase the risk of infection. These drugs may introduce the confounding factors in these results. Since the detailed information on individuals previously exposed to these drugs was unavailable to us, it is difficult to perform further sensitivity analysis.

Above all, this meta-analysis showed that biological therapy in patients with SpA may increase the risk of infections, including serious infections, URTI, nasopharyngitis, and *Candida* infection, and JAK inhibitors had an increased risk of herpes zoster in patients with peripheral SpA, which should be paid attention in our clinical practice. These findings have direct implications in the management of many patients treated currently with biologics and a small molecule targeted drugs. Physicians should weigh the benefits and risks of treatments while making decisions. In addition, more studies, with a larger population and longer follow-up and in the real-world setting, will be needed to fully elucidate the safety profile of biologics and small molecule targeted drugs.

Conflicts of interest

None.

References

- 1. MacMillan A, Corser A, Clark Z, McCrum C, Gaffney K. Masterclass: axial spondyloarthritis for osteopaths and manual therapists. Int J Osteopath Med 2021;41:45–56. doi: 10.1016/j. ijosm.2021.03.005.
- Huang F, Sun F, Wan WG, Wu LJ, Dong LL, Zhang X, et al. Secukinumab provided significant and sustained improvement in the signs and symptoms of ankylosing spondylitis: results from the 52 week, phase III China-centric study, MEASURE 5. Chin Med J 2020;133:2521–2531. doi: 10.1097/CM9.000000000001099.
- Chen M, Dai SM. A novel treatment for psoriatic arthritis: Janus kinase inhibitors. Chin Med J 2020;133:959–967. doi: 10.1097/ cm9.000000000000711.
- 4. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. doi: 10.1136/bmj.b2535.
- Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:14898. doi: 10.1136/bmj.14898.
- 6. Mandour M, Chen S, van de Sande MGH. The role of the IL-23/IL-17 axis in disease initiation in spondyloarthritis: lessons learned from animal models. Front Immunol 2021;12:618581. doi: 10.3389/fimmu.2021.618581.
- Vecellio M, Hake VX, Davidson C, Carena MC, Wordsworth BP, Selmi C. The IL-17/IL-23 axis and its genetic contribution to psoriatic arthritis. Front Immunol 2020;11:596086. doi: 10.3389/ fimmu.2020.596086.
- Li LL, Dai B, Sun YH, Zhang TT. The activation of IL-17 signaling pathway promotes pyroptosis in pneumonia-induced sepsis. Ann Transl Med 2020;8:674. doi: 10.21037/atm-19-1739.
- Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, et al. Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae. J Exp Med 2005;202:761–769. doi: 10.1084/jem.20050193.
- Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, *et al*. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med 2008;14:275–281. doi: 10.1038/nm1710.
 Zhang X, Gao L, Lei L, Zhong Y, Dube P, Berton MT, *et al*. A
- 11. Zhang X, Gao L, Lei L, Zhong Y, Dube P, Berton MT, et al. A MyD88-dependent early IL-17 production protects mice against airway infection with the obligate intracellular pathogen Chlamydia muridarum. J Immunol 2009;183:1291–1300. doi: 10.4049/ jimmu- nol.0803075.
- Lin Y, Ritchea S, Logar A, Slight S, Messmer M, Rangel-Moreno J, et al. Interleukin-17 is required for T helper 1 cell immunity and host resistance to the intracellular pathogen Francisella tularensis. Immunity 2009;31:799–810. doi: 10.1016/j.immuni.2009.08.025.
- Conti HK, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med 2009;206:299–311. doi: 10.1084/jem.20081463.
- Eyerich K, Foerster S, Rombold S, Seidl HP, Behrendt H, Hofmann H, *et al.* Patients with chronic mucocutaneous candidiasis exhibit reduced production of Th17-associated cytokines IL-17 and IL-22. J Invest Dermatol 2008;128:2640–2645. doi: 10.1038/jid. 2008.139.
- 15. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. 2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and treatment network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Care Res (Hoboken) 2019;71:1285–1299. doi: 10.1002/acr.24025.
- 16. Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and metaanalysis of randomised placebo-controlled trials. Ann Rheum Dis 2010;69:1756–1761. doi: 10.1136/ard.2008.098822.
- 17. Wang S, He Q, Shuai Z. Risk of serious infections in biological treatment of patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Clin Rheumatol 2017;37:439–450. doi: 10.1007/s10067-017-3966-1.

- Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of Janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology 2020;158:1554–1573. doi: 10.1053/j. gastro.2020.01.001.
- Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, *et al.* Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66:2675–2684. doi: 10.1002/art.38745.
- Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, *et al.* Longterm safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open 2020;6:e001395. doi: 10.1136/rmdopen-2020-001395.
- 21. Kremer J, Bingham C, Cappelli L, Etzel C, Kavanaugh A. OP0028 post-approval comparative safety study of tofacitinib and biologic DMARDs: five-year results from a US-based rheumatoid arthritis registry. Ann Rheum Dis 2019;78 (Suppl 2):82–83. doi:10.1136/ annrheumdis-2019-eular.621.
- 22. Wang F, Sun L, Wang S, Davis JM 3rd, Matteson EL, Murad MH, et al. Efficacy and safety of tofacitinib, baricitinib, and upadacitinib for rheumatoid arthritis: a systematic review and meta-analysis. Mayo Clin Proc 2020;95:1404–1419. doi: 10.1016/j.mayocp. 2020.01.039.
- 23. van Vollenhoven RF, Tanaka Y, Lamba M, Collinge M, Hendrikx T, Hirose T, *et al.* THU0178 relationship between NK cell count and important safety events in rheumatoid arthritis patients treated with tofacitinib. Ann Rheum Dis 2015;74:258. doi: 10.1136/annrheum-dis-2015-eular.3674.

How to cite this article: Hu L, Man S, Ji X, Wang Y, Liu X, Zhang J, Song C, Zhu J, Huang F. Risk of infections of biological and targeted drugs in patients with spondyloarthritis: meta-analysis of randomized clinical trials. Chin Med J 2022;135:911–919. doi: 10.1097/CM9.00000000001928